

Per Examiner's request, proposed formal drawing is submitted herewith along with a marked up version showing the changes. Please substitute the enclosed formal drawing for the originally submitted drawing. No new matter is contained in the formal drawing.

Status of the claims

Claims 10-14 and 21 are rejected per 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claims 10-14 and 21 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 10-13 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Darnell et al. ("Darnell") (Molecular Cell Biology, Scientific American Books, copyright 1986, pages 1095-1101). Claims 10-13 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Pokkuluri et al. ("Pokkuluri") (Structure, 15 August 1998, 6, pp 1067-1073).

Claims 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pokkuluri et al. or Darnell et al. in view of Goling ("Goling") (Journal of Immunology, 1980, 124(5), pp 2082-2088) and Skoog et al. ("Skoog") (Scand. J. Immunology, 1980, 11(4), pp 369-376).

Amendment of the claims

Per the Examiner's suggestion, independent claim 10 has been amended to clarify that both the antigen binding sites and the complementary determining segments are positioned at opposite ends of the molecule. In addition, per Examiner's suggestion, the "unnatural configuration" language of independent claim 10 has been replaced with "counterpoised."

Applicants were invited to point out support for the "bound to" language of claim 10 in the disclosure. Such support can be found in, for example, Figures 2 and 4, which clearly depict the bivalent detector molecule of the present invention, including two antigen binding regions contiguous with the two antigen non-binding regions of the molecule. Further support can be found in the specification at, for example, page 9, lines 8-9, where

it is stated that "a peptide linker joins the C-terminus of one V_L gene to the N-terminus of a second V_L gene." Claim 10 has been amended accordingly.

Claim 10 has been further amended to recite an isolated molecule consisting of two variable light chains. Support for said recitation can be found in the specification at, for example, page 5, lines 6-7.

Applicants have added new claims 22-38. Support for newly added claim 22 can be found in the specification at, for example, page 9, lines 8-9.

Support for newly added claim 23 can be found in the specification at, for example, page 5, line 8.

Support for newly added claim 24 can be found in the specification at, for example, page 10, lines 9-14.

Support for newly added claim 25 can be found in the specification at, for example, page 7, lines 26-27.

Support for newly added claim 26 can be found in the specification at, for example, page 11, line 25.

Support for newly added claim 27 can be found in the specification at, for example, page 8, lines 3-4, and page 11, lines 23-25.

Support for newly added claim 28 can be found in the specification at, for example, page 11, line 26.

Support for newly added claim 29 can be found in the specification at, for example, page 8, lines 2-4.

Support for newly added claim 30 can be found in the specification at, for example, page 11, lines 28-29.

Support for newly added claim 31 can be found in the specification at, for example, page 12, line 1.

Support for newly added claim 32 can be found in the specification at, for example, page 6, lines 5-7.

Support for newly added claim 33 can be found in the specification at, for example, page 10, lines 9-14.

Support for newly added claim 34 can be found in the specification at, for example, page 8, line 3.

Support for newly added claim 35 can be found in the specification at, for example, page 8, line 3.

Support for newly added claim 36 can be found in the specification at, for example, page 6, lines 7-8.

Support for newly added claim 37 can be found in the specification at, for example, page 15, lines 12-13.

Support for newly added claim 38 can be found in the specification at, for example, page 15, lines 15-17.

Section 112 rejections are obviated in light of the amendments to claim 10.

Per Examiner's suggestions to amend parts of claim 10 and due to the amendments to claim 10 described supra, withdrawal of the 35 U.S.C. §112, first paragraph and second paragraph rejections is hereby solicited. Because of the dependency on claim 10 and in light of changes made to claim 10, claims 11-14 and 21 need not be amended. The §112 rejection pertaining to these claims is obviated.

Claim 10 is allowable over Darnell.

Claims 10-13 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Darnell et al. Reconsideration of the claims is requested in light of the amendment to claim 10 and the following argument.

Claim 10 has been amended to recite an "isolated molecule . . . consisting of a purified first moiety containing a first antigen binding region . . . and a purified second moiety containing a second antigen-binding region . . . wherein the first moiety and the second moiety are light chain variable domains."

Darnell does not disclose a molecule consisting solely of two light chain variable domains. In fact, Darnell necessitates the presence of heavy chains in every antibody, "Each antibody molecule has two chains, a *light (L) chain . . . and a heavy (H) chain . . .*" See *Darnell*, at p. 1095, 2nd column (emphasis in original); see also *Id.* at p.

1096, 1st column ("Every . . . antibody molecule has one type of L chain and one type of H chain."); see also *Id.* at Fig. 24-16 (depicting an antibody molecule consisting of two heavy chains and two light chains).

Furthermore, the antigen-biding regions disclosed in the present invention are not of the same type as the antigen-binding regions disclosed in Darnell. Darnell states that

"[b]oth the correct L chain and the correct H chain are needed to get . . . binding specificity. Thus, it is the joint structure formed by two variable regions that produces a binding site and not either variable region alone."

See *Id.* at p. 1097, 1st column. Unlike Darnell, the instant invention does not require the use of a heavy chain. Hence, the binding sites of the instant invention cannot be formed by the variable regions of the light and the heavy chains.

In fact, substituting Darnell's heavy chain for a light chain would render Darnell useless. In the antibody of the type disclosed in Darnell (see, e.g., Fig. 24-16) two light chains simply cannot form a stable molecule. Hence, Darnell requires a light chain and a heavy chain for antibody formation and stability. In the present invention, in effect, a heavy chain is replaced by a light chain, and a stable antibody consisting of two light chain variable domains results. Such a substitution makes the present invention non-obvious over Darnell. See *in re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) (If the teachings of a prior art reference would lead one skilled in the art to make a modification which would render that prior art inoperable, then such a modification would generally not be obvious).

In conclusion, claim 10 is allowable over Darnell because Darnell does not disclose an isolated molecule consisting solely of two variable light chain domains. Because Darnell necessitates the use of heavy chains in antibodies, it teaches away from the present embodiment and does not anticipate claim 10.

Claims 11-13 and 21 are allowable over Darnell.

Claims 11-13 and 21 depend on claim 10 and are therefore allowable over Darnell. Claim 11 is allowable for the additional reason in that it recites the use of two variable light chains in the construction of the molecule described in claim 10. The molecule in Darnell always possesses heavy chains as well as light chains. Because there are no heavy

chains in the present invention, claim 11 is allowable over Darnell.

Claim 21 is allowable for the additional reason in that it recites an antigen bidding site that comprises a complementary determining region and a framework region of a variable light chain domain. In contrast, the antigen bidding site disclosed in Darnell is formed by the variable region of a light chain and the variable region of a heavy chain. See *Id.* at p. 1097, 1st column. Darnell further states that a bidding site cannot be formed by a single variable region. *Id.* In the present invention, an antigen binding region is formed from the folding of a single variable light chain. For the foregoing reasons, claim 21 is allowable over Darnell.

Pokkuluri cannot be used as prior art under section 102(b).

Claims 10-13 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Pokkuluri. The inventor of the instant application is a co-author to the Pokkuluri reference, with said reference published on August 15, 1998. The instant application was filed on August 5, 1999, less than one year after the publication date of the cited reference. As such, the Applicants submit that the Pokkuluri reference does not act as prior art against the instant application.

Pokkuluri is not prior art under section 102(a).

Claims 10-13 and 21 are rejected under 35 U.S.C. 102(a) as being anticipated by Pokkuluri. On July 03, 2002, the inventor Fred J. Stevens filed an affidavit under 37 C.F.R. 1.131, swearing behind the publication date of the Pokkuluri reference. The Examiner found the affidavit ineffective. The Examiner indicated that the invention report disclosed Janusbody constructs, and that Janusbodies were not recited in the instant claims. Per this indication, a new claim reciting Janusbodies has been added. In addition, the Official Action in this matter stated that the limitations reciting binding site and CDR positioning within the Janusbody were not disclosed in the invention report.

Two inventors of the instant application file herewith additional antedating 37 CFR 1.131 affidavits stating that the instant application was reduced to practice at least as early as March 10, 1998. Attached to each of the affidavits is an intra-laboratory memo from Argonne National Laboratories, dated March 10, 1998. The memo is accompanied by an

invention disclosure form relating to the instant invention. The invention disclosure form was signed by two co-inventors on May 11, 1998. On page 3, 3rd paragraph (tabbed and circled in the enclosed memorandum), of the aforementioned memo, the inventors disclose the following:

Crystallographic analysis demonstrated an unexpected arrangement of domains in the dimer. Instead of the typical dimer motif, in which the complementarity determining segments (CDRs) responsible for interaction are arranged in a juxtaposed position, the domains in the high-affinity dimer were counterpoised. Each set of CDR segments (three per domain) were positioned at opposite ends of the dimeric assembly. In this orientation they were paired with turns contributed by conserved "framework" portions of the domain resulting in a potential antigen binding surface comparable in size to that of an antibody.

This language recites the binding site and CDR positioning within the Janusbody constructs, as requested by the Examiner in the present official action. The intra-laboratory memorandum, as well as the invention disclosure form, were inadvertently left out of the enclosure provided with the July 3, 2002 1.131 affidavit.

The 1.131 affidavits in their present form effectively swear behind the publication date of the cited Pokkuluri reference. As such, the Applicants submit that the Pokkuluri reference does not act as prior art against the instant application.

Claim 14 is allowable over Pokkuluri or Darnell in view of Goling and Skoog.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pokkuluri et al. or Darnell et al. in view Goling and Skoog et al. As stated above, because the Pokkuluri reference cannot be cited as prior art, the Applicants submit that the reference cannot be used to form an obviousness rejection. Further, for reasons stated *supra*, any rejections based on Darnell are obviated.

Furthermore, claim 14 depends on claim 10 and is therefore allowable. Claim 14 is allowable for the additional reason in that it recites a molecular weight of between 20,000 and 30,000 daltons. Darnell recites antibodies having two chains, a light chain with a molecular weight of about 23,000 daltons and a heavy chain with a molecular weight of about 53,000 daltons. See *Darnell*, at p. 1095, 2nd column. Hence, the combined weight

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of an antibody molecule according to Darnell is at least 76,000 daltons, well outside of the recited molecular weight range of the Janusbody construct.

Although Goling and Skoog teach protein structures of 20,000 to 30,000 daltons, neither Goling or Skoog teach a structure composed solely of two light chain domains, as recited in the present invention. In addition, neither Goling nor Skoog teach the light chain dimers containing two antigen binding sites positioned at opposite ends of the molecule. Hence, claim 14 is allowable.

CONCLUSION

Applicants submit that in light of the foregoing amendments and remarks thereto, the application is deemed in order for allowance.

An earnest attempt has been made hereby to respond to the §102, §103 and §112 rejections contained in the July 15, 2002 official action. Applicants submit that the instant amendment places the application in condition for allowance. If the Examiner feels that a telephonic interview will expedite allowance of the Application, she is respectfully urged to contact the undersigned. Reconsideration and allowance of claims 10-14 and 21 and allowance of new claims 22-38 is hereby solicited.

Respectfully submitted,

CHERSKOV & FLAYNIK

By


Michael J. Cherskov (33,664)

10. (Thrice Amended) An isolated molecule containing two antigen binding sites and complementary determining segments, both the antigen binding sites and the complementary determining segments positioned at opposite ends of the molecule, the molecule [comprising] consisting of:

a) a purified first moiety containing a first antigen binding region bound to a first antigen non-binding region via a peptide linker; and

b) a purified second moiety containing a second antigen-binding region bound to a second antigen-non-binding region via a peptide linker, whereby the moieties are engineered so as to be juxtaposed to each other in [an unnatural] a counterpoised configuration, [and] wherein the first moiety and second moiety are derived from the same gene, and wherein the first moiety and the second moiety are light chain variable domains.

22. (New) The molecule as recited in claim 10, wherein the peptide linker joins the C-terminus of one variable light chain domain to the N-terminus of a second variable light chain domain.

23. (New) The molecule as recited in claim 10, wherein the molecule is a Janusbody construct.

24. (New) The molecule as recited in claim 10, wherein the molecule is a dimer of variable light chains selected from the group consisting of Len, Rec, Jto, Wil, Loc, Wat, Cle, Rhe, and combinations thereof.

25. (New) The molecule as recited in claim 10, wherein the counterpoised configuration of the first and second moieties is the result of amino acid substitutions at specific sites.

26. (New) The molecule as recited in claim 24, wherein the counterpoised configuration of the first and second moieties is due to excess negative charge at the modified site.

27. (New) The molecule as recited in claim 24, wherein the amino acid substitution is replacement of glutamine 38 with glutamic acid.

28. (New) The molecule as recited in claim 24, wherein the amino acid substitution is replacement of lysine 30 with threonine.

29. (New) The molecule as recited in claim 24, wherein the dimer formation is achieved by mutations selected from the group of amino acid substitutions comprising substituting lysine 30 with threonine, glutamine 89 with alanine, glutamine 89 with leucine, glutamine 38 with glutamic acid, and combinations thereof.

30. (New) The molecule as recited in claim 27, wherein the two moieties have an association constant of approximately $5.8 \times 10^5 \text{ M}^{-1}$.

31. (New) The molecule as recited in claim 28, wherein the two moieties have an association constant of approximately $0.8 \times 10^5 \text{ M}^{-1}$.

32. (New) An isolated molecule consisting of two light chain variable domains, the said light chain variable domains being modified light chain variable domains from immunoglobulin molecules, wherein the said modification is replacement of an acidic amino acid with a hydrophobic amino acid.

33. (New) The molecule as recited in claim 32, wherein the light chain variable domains are immunoglobulin molecules selected from the group consisting of Len, Rec, Jto, Wil, Loc, Wat, Cle, Rhe, and combinations thereof.

34. (New) The molecule as recited in claim 32, wherein the modification is replacement of glutamine 89 with alanine.

35. (New) The molecule as recited in claim 32, wherein the modification is replacement of glutamine 89 with leucine.

36. (New) The molecule as recited in claim 32, wherein the addition of the hydrophobic amino acid results in two to three orders of magnitude increased affinity between the dimer subunits, compared to the affinity between natural dimer subunits.

37. (New) The molecule as recited in claim 34, wherein the two variable light chains have an association constant approximately greater than 10^8 M^{-1} .

38. (New) The molecule as recited in claim 35, wherein the two variable light chains have an association constant of approximately $4 \times 10^6 \text{ M}^{-1}$.